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RESEARCH ARTICLE

Sex-Differences in the Metabolic Health of Offspring of Parents with Diabetes: A Record-Linkage Study

Marian C. Aldhous^{1*}, Rebecca M. Reynolds², Archie Campbell³, Pamela Linksted³, Robert S. Lindsay⁴, Blair H. Smith⁵, Jonathan R. Seckl², David J. Porteous^{3,6}, Jane E. Norman¹, Generation Scotland^{3,7¶}



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Data Availability Statement: The anonymised data used in this study were obtained from Generation Scotland (GS). GS data are available for medical research on application to the GS Access Committee. Details of access to GS data are available on the "Access" page of the Generation Scotland website: <http://www.generationscotland.org>.

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1 Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom, **2** Endocrinology Unit, University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom, **3** Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics & Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom, **4** British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom, **5** Medical Research Institute, University of Dundee, Dundee, United Kingdom, **6** Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom, **7** Generation Scotland: A Collaboration between the University Medical Schools and NHS in Aberdeen, Dundee, Edinburgh and Glasgow, Scotland, United Kingdom

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* M.Aldhous@ed.ac.uk

Abstract

Maternal diabetes in pregnancy affects offspring health. The impact of parental diabetes on offspring health is unclear. We investigated the impact of parental diabetes on the metabolic-health of adult-offspring who did not themselves have diabetes. Data from the Generation Scotland: Scottish Family Health Study, a population-based family cohort, were record-linked to subjects' own diabetes medical records. From F_0 -parents, we identified F_1 -offspring of: mothers with diabetes (OMD, $n = 409$), fathers with diabetes (OFD, $n = 468$), no parent with diabetes (ONoPD, $n = 2489$). Metabolic syndrome, body, biochemical measurements and blood-pressure were compared between F_1 -offspring groups by sex. A higher proportion of female OMD had metabolic syndrome than female OFD or ONoPD ($P < 0.0001$). In female offspring, predictors of metabolic syndrome were: having a mother with diabetes ($OR = 1.78$, $CI 1.03-3.07$, [reference ONoPD]), body mass index (BMI, $OR = 1.21$, $CI 1.13-1.30$) and age ($OR = 1.03$, $CI 1.01-1.06$). In male offspring, predictors of metabolic syndrome were: BMI ($OR = 1.18$, $CI 1.09-1.29$) and percent body-fat ($OR = 1.12$, $CI 1.05-1.19$). In both sexes, OMD had higher blood-pressure than OFD ($P < 0.0001$). In females, OMD had higher glucose ($P < 0.0001$) and percent body-fat ($P < 0.0001$) compared with OFD or ONoPD. OMD and OFD both had increased waist-measurements ($P < 0.0001$), BMI ($P < 0.0001$) and percent body-fat ($P < 0.0001$) compared with ONoPD. Female OMD and OFD had lower HDL-cholesterol levels ($P < 0.0001$) than female ONoPD. Parental diabetes is associated with higher offspring-BMI and body-fat. In female offspring, maternal diabetes increased the odds of

Scottish Government [grant no. CZH/4/881] and Tommy's the Baby Charity. The funders made no contribution to the study design or execution. Generation Scotland has received core funding from the Chief Scientist Office of the Scottish Government Health Directorates [grant no. CZD/16/6] and the Scottish Funding Council [grant no. HR03006]. The authors are grateful to all the families who took part, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants and nurses. Data are available for analysis by members of the Scottish Diabetes Research Network (SDRN) thanks to the hard work and dedication of NHS staff across Scotland who enter the data and people and organizations (the Scottish Care Information -Diabetes Collaboration [SCI-DC] Steering Group, the Scottish Diabetes Group, the Scottish Diabetes Survey Group, the managed clinical network managers and staff in each Health Board) involved in setting up, maintaining and overseeing SCI-DC. The SDRN receives core support from the Chief Scientist's Office at the Scottish Government Health Department. This work was supported by the Wellcome Trust through the Scottish Health Informatics Programme (SHIP) Grant [Ref WT086113]. SHIP is a collaboration between the Universities of Aberdeen, Dundee, Edinburgh, Glasgow and St Andrews and the Information Services Division of NHS Scotland.

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metabolic syndrome, even after adjusting for BMI. Further investigations are required to determine the mechanisms involved.

Introduction

Population-rates of diabetes and obesity have risen in recent years [1]. Obesity increases the risk of type-2 diabetes mellitus (T2DM); having a parent with diabetes increases the risks of later obesity, T2DM and/or cardiovascular problems in their children [2–4]. Maternal diabetes during pregnancy, whether pre-existing type-1 diabetes mellitus (T1DM), T2DM or gestational diabetes mellitus (GDM, first diagnosed during pregnancy) has long-term health-effects on the offspring. Such offspring have higher birth-weights [5–7] and increased adiposity during childhood compared with offspring of mothers without diabetes [8,9]. In contrast, children of fathers with diabetes have lower birth-weights [10,11]. In Scotland, ~5% of women of reproductive age have been diagnosed with diabetes [12], which may impact childhood obesity-rates and health. As childhood obesity-rates are already high (16.8% in Scotland in 2012 [13]) this raises public-health concerns.

The longer-term health-effects of parental diabetes on adult offspring are less clear. Increased body mass index (BMI) was seen in 18 year-old boys exposed to intrauterine maternal diabetes compared with their older brothers, who were born before their mothers developed diabetes [14]. However, there are few studies of long-term effects of maternal diabetes diagnosed after pregnancy or paternal diabetes on adult offspring and few data comparing the impact of paternal with maternal diabetes.

The Generation Scotland: Scottish Family Health Study (GS:SFHS) is a family-based population cohort, recruited to investigate the genetic and environmental factors involved in the aetiology of various complex diseases common in Scotland [15,16]. The known extended family-relationships within GS:SFHS also allow for investigations of any trans-generational effects of grandparental T2DM. Having a grandparent with diabetes has been associated with children being overweight aged 4 years [17], but there is little information on any long-term effects into adulthood.

The primary aim of this study was to determine, in adults without diabetes, the long-term metabolic health-effects of having a mother with diabetes compared with having a father with diabetes and no parent with diabetes. Specifically, we determined the frequency of metabolic syndrome (MetS) and the relative contributions of body and biochemical measurements, blood-pressure and social factors. The secondary aims were to investigate whether intrauterine exposure to maternal diabetes had any additional effect on offspring health compared with having a mother with diabetes diagnosed after pregnancy, and to investigate whether having a grandparent with diabetes affected body, biochemical measurements, or blood-pressure of their grandchildren through specific maternal- or paternal-lineages.

Methods

Generation Scotland: Scottish Family Health Study Cohort

GS:SFHS participants were recruited from the Scottish general population during 2006–2011, via primary-care physicians and publicity across Scotland, resulting in 23,960 people in family groups. Potential study participants were screened to exclude those with serious terminal illness or inability to give informed consent (~5% excluded). At recruitment into GS:SFHS, participants gave written consent, completed a detailed health and social questionnaire and

attended a research clinic for clinical examination, body measurements and collection of fast-ing blood samples. Details of the GS:SFHS cohort and the data-collection processes are published elsewhere [15,16] and via links from the “GS Resources” page of the Generation Scotland website (www.generationscotland.org). GS data are available for medical research on application to the GS Access Committee. Details of access to GS data are available on the “Access” page of the Generation Scotland website. This was a data-linkage analysis, so no new data were collected for this study.

Approvals

For this study, only those GS:SFHS participants who had given written consent for record-linkage of their GS:SFHS data to their own medical records were used. Ethical approval for the record-linkage was obtained from the East of Scotland Research Ethics Committee (reference 10/S1402/20). Permissions for use of NHS health data in this record-linkage were obtained from the NHS Privacy Advisory Committee, Scottish Diabetes Research Network and Caldicott Guardians for Scotland.

Record linkage process

Data were linked to records for diabetes diagnoses at any time-point to November 2011 (via the Scottish Care Information Diabetes Collaboration [SCI-DC, <http://www.sci-diabetes.scot.nhs.uk/>]) and pregnancy/birth records (Scottish Morbidity Report 02 [SMR02] from Information Services Division [ISD], NHS Scotland). To safeguard subject confidentiality, data were linked through the Health Informatics Centre (HIC) Dundee and ISD. The record-linkage process is summarized in Fig 1, showing identification of subjects at each stage and final numbers for each subject group. GS:SFHS ID-numbers for participants with F_0 -parents and/or F_1 -offspring within GS:SFHS were sent to HIC, where participant NHS-health numbers were identified, assigned new ID-numbers and sent to ISD for record-linkage. GS:SFHS pedigree tables were used to identify F_0 -parents, F_1 -offspring and F_2 -grandchildren.

GS:SFHS data analysed

Data were obtained at recruitment into GS:SFHS [16], from direct measurement (body, biochemistry, and blood-pressure) or questionnaire (comorbidity information for self and family members, family relationships, smoking status and postcode at recruitment). Over 95% of participants were Caucasian. Parameters analysed were:

Body measurements. height, weight, BMI, waist, hips, waist: hip ratio (WHR), percent body-fat, systolic and diastolic blood-pressure (both mean of two measurements).

Blood biochemical measurements. sodium, potassium, urea, creatinine, glucose, total cholesterol, HDL-cholesterol, total: HDL cholesterol ratio (THCR).

Diseases diagnosed. diabetes, asthma, depression, *cardiovascular disease* (heart disease, hypertension, stroke); *bone disease* (osteoarthritis, rheumatoid arthritis, hip fracture).

Smoking data. smoking status at recruitment (current, non-smokers, ex-smokers); exposure to other peoples' smoke.

Scottish Index of Material Deprivation (SIMD). categorized in quintiles (1 [most deprived] to 5 [least deprived], from 2009) for each subject's home postcode at recruitment (<http://www.scotland.gov.uk/Topics/Statistics/SIMD>).

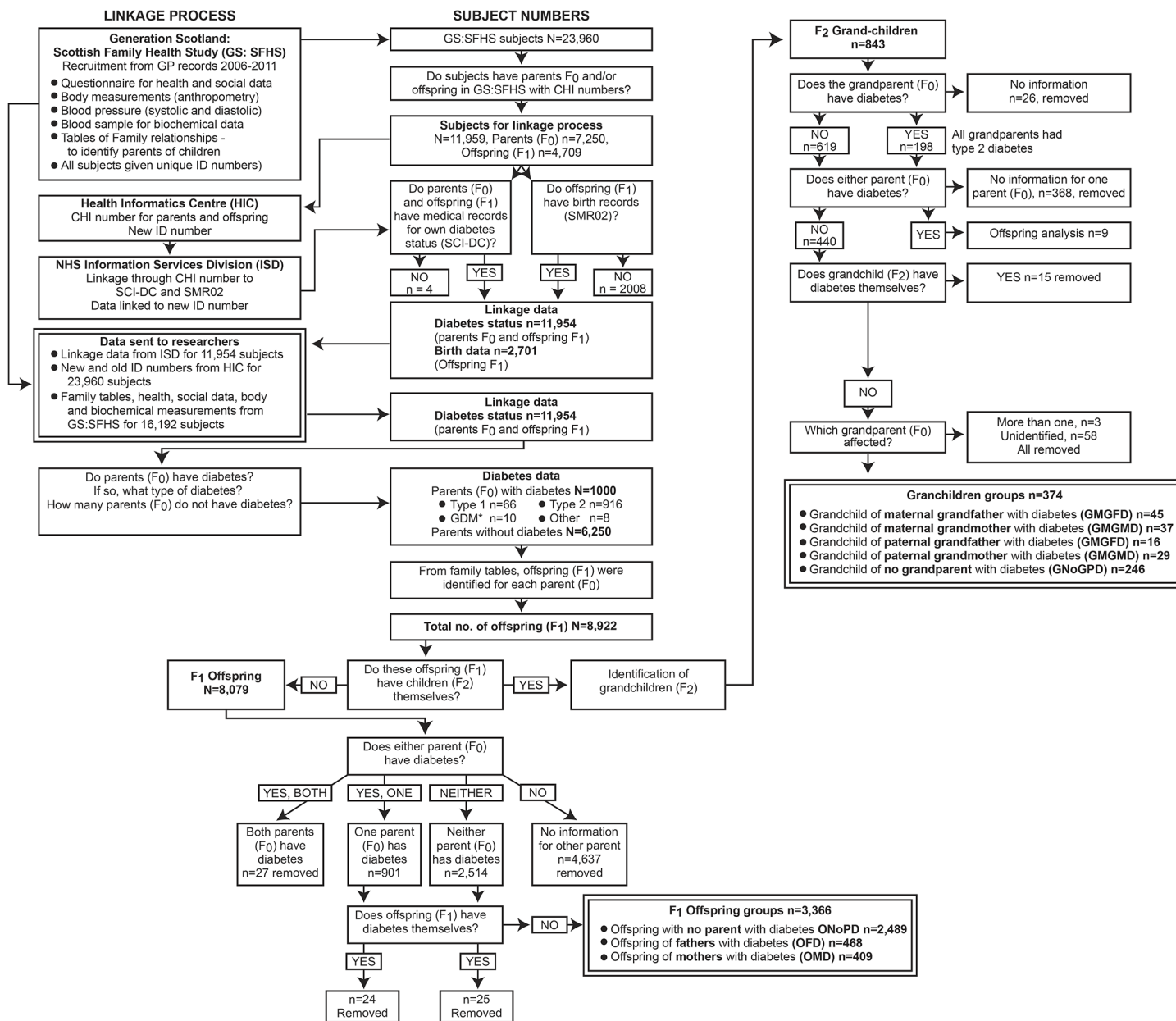


Fig 1. Summary of the linkage process and identification of the F₁-offspring and F₂-grandchildren groups for analysis. Linkage process of GS:SFHS data. Subjects who had children or parents within the GS:SFHS cohort and had health numbers were sent via HIC to ISD for linkage to their own diabetes and birth medical records. From the diabetes-linked data, the F₁-offspring of the F₀-parents with or without diabetes were identified. F₁-offspring who had children of their own were separated for analysis of the effects of grandparental diabetes on F₂-grandchildren. F₁-offspring groups were defined by whether their mother (OMD) or father (OFD) or no parent had diabetes (ONoPD). F₂-grandchildren groups with grandparents with diabetes were grouped by maternal or paternal lineage: grandchild of maternal grandmother with diabetes (GMGMD), grandchild of maternal grandfather with diabetes (GMGFD), grandchild of paternal grandmother with diabetes (GPGMD), grandchild of paternal grandfather with diabetes (GPGFD), or grandchild of grandparents with no diabetes (GNoGPD). * Mothers who developed GDM during pregnancy were identified from SMR02

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Identification of F₁-offspring and F₂-grandchildren of F₀-parents with diabetes

From SMR02 data, we identified F₁-offspring whose F₀-mothers developed GDM during the index pregnancy (n = 10) and so were exposed *in utero* (EIU) to maternal diabetes. From

SCI-DC data, we obtained diabetes diagnoses (with type and dates) for all subjects in the record-linkage, i.e. a diagnosis (or no diagnosis) of diabetes in the subjects' own medical records. Offspring whose mothers had pre-existing T1DM ($n = 8$) during the index pregnancy were also included in the EIU group. No mothers had developed T2DM prior to the index pregnancy. Due to small numbers, the EIU group was combined with those whose mothers developed diabetes after pregnancy as F₁-offspring of mothers with diabetes (OMD) for all analyses: OMD were compared with F₁-offspring of fathers with diabetes (OFD) and F₁-offspring of no parent with diabetes (ONoPD).

The GS:SFHS questionnaire asked whether the subject or family members had diabetes: F₁-offspring ($n = 49$) or F₂-grandchildren ($n = 5$) who had diabetes themselves were removed because we aimed to investigate the effect of familial diabetes on the subjects' health, which might be obscured by subjects' own diabetes disease-processes. F₁-offspring with both F₀-parents with diabetes ($n = 27$) and F₂-grandchildren with more than one F₀-grandparent with diabetes ($n = 3$) were removed. Neither F₁-parent of the F₂-grandchildren had diabetes. Siblings were included but known twins were removed.

F₁-offspring were grouped according to parental diabetes status:

F₁-offspring of mothers with diabetes: (OMD, $n = 409$) those whose mothers were diagnosed with diabetes;

F₁-offspring of fathers with diabetes: (OFD, $n = 468$) those whose fathers were diagnosed with diabetes;

F₁-offspring of no parent with diabetes: (ONoPD, $n = 2,489$) those for whom neither parent had diabetes.

F₂-grandchildren were grouped according to parental lineage:

F₂-Grandchildren of maternal grandfather with diabetes: (GMGFD, $n = 45$)

F₂-Grandchildren of maternal grandmother with diabetes: (GMGMD, $n = 37$)

F₂-Grandchildren of paternal grandfather with diabetes: (PGGFD, $n = 16$)

F₂-Grandchildren of paternal grandmother with diabetes: (PGGMD, $n = 29$)

F₂-Grandchildren of grandparents with no evidence of diabetes: (GNoGPD, $n = 246$).

Definition of Metabolic Syndrome (MetS)

The International Diabetes Federation definitions (from 2009 [18]) were used to define those with MetS. Using these criteria, subjects were defined as having MetS if three of five criteria are present:

- Central obesity: a waist measurement of ≥ 94 cm in males and ≥ 80 cm in females;
- Reduced HDL-cholesterol: ≤ 1.0 mmol/L (40mg/dL) in males and ≤ 1.3 mmol/L (50mg/dL) in females;
- Elevated blood-pressure: systolic ≥ 130 and/or diastolic ≥ 85 mm Hg and/or being treated with anti-hypertensive drugs;
- Raised glucose levels: ≥ 5.6 mmol/L (100mg/dL);
- Elevated triglyceride levels: > 1.7 mmol/L (150mg/dL).

Triglyceride levels were not available for our subjects: hence if subjects met only two (of four) criteria they were assumed not to have MetS. Where values for any other criteria were missing, subjects were only included if the three remaining criteria were all outside the thresholds for MetS (i.e. had MetS) or were all within normal values (i.e. did not have MetS).

Statistical analysis

To investigate the relationships of different parameters in the F₁-offspring or F₂-grandchildren groups, Kruskal-Wallis tests were used to analyse continuous measurements. Chi-squared tests were used for categorical data and Spearman tests were used for correlations; statistical significance was set at $P < 0.05$. Given the major effect of sex of the subjects on the outcomes of interest, all analyses were performed subdivided by sex of offspring or grandchildren. Rest of cohort (RoC, GS:SFHS subjects without diabetes excluded from the study groups) data were included in the graphs to show the representativeness of the offspring data. MetS was compared between the F₁-offspring groups by sex.

To determine the predictors of MetS, relevant body and biochemical measurements, F₁-offspring group (ONoPD as reference), age (continuous variable), smoking, SIMD (quintile 5 as reference), whether a sibling was in the study (yes/no) were used in forwards and backwards stepwise logistic regression (alpha of 0.5) to identify factors associated with MetS. Statistical analyses used GraphPad Prism6 (GraphPad Software) and Minitab 16 Statistical Software (Minitab Inc.).

Results

Record-linkage

Diabetes-linked data were obtained for 11,954 GS:SFHS subjects. SMR02 provided data for F₁-offspring and F₂-grandchildren (born 1980–1992) for whether their mother had GDM, their mother's age at pregnancy, mother's height, SIMD quintile at birth, birth-weight (not adjusted for gestational age), year and month of birth (for season of birth); data on their mother's smoking history were incomplete and not used; the mother's weight or BMI at pregnancy were not recorded in SMR02 at that time.

Demographics, comorbidity, social and birth data

Demographic, comorbidity, social and birth data were compared by sex between F₁-offspring groups (Table 1). The median age of all the F₁-offspring was 33 years (interquartile range [IQR] 26–40 years). OMD and OFD were significantly older than ONoPD (Kruskal-Wallis, $P < 0.0001$ for both sexes). There were no differences between F₁-offspring groups in the proportion of subjects who had siblings in the study for either sex.

Comorbidity. Differences in proportions of subjects with other diseases were seen between the F₁-offspring groups in both males and females ($P < 0.0001$). Higher percentages of OMD had cardiovascular disease than OFD and ONoPD ($P < 0.0001$ for both sexes). In females, but not males, higher percentages of OMD and OFD than ONoPD had depression ($P = 0.0135$) or bone disease ($P < 0.0001$).

Smoking. Smoking status differed between the groups in males ($P = 0.0298$) and females ($P = 0.0234$), as higher percentages of OMD and OFD were current smokers than ONoPD. A higher proportion of OMD than OFD or ONoPD were exposed to other peoples' smoke in males ($P = 0.0230$) and females ($P = 0.0306$).

Table 1. Demographics, comorbidity, social/lifestyle and birth data for male and female F₁-offspring.

	Males in F ₁ -Offspring groups			X ²	P value	Females in F ₁ -Offspring groups			X ²	P value
	OMD	OFD	ONoPD			OMD	OFD	ONoPD		
Demographic data	N = 164	N = 194	N = 1078			N = 245	N = 274	N = 1411		
Sex (% group)	40.1	41.5	43.3			59.9	58.5	56.7	1.807	0.4051 ^a
Age (years):										
Median	40.0	35.0	31.0		<0.0001 ^b	39.0	36.0	32.0		<0.0001 ^b
IQR ^c	31.3–48.0	28.0–43.0	25.0–38.0			31.5–46.0	28.0–42.0	25.0–39.0		
Range	18–61	18–61	18–60			18–65	18–59	18–62		
No. (%) aged 18–29	32 (19.5)	54 (27.8)	446 (41.4)			50 (20.4)	81 (29.6)	561 (39.8)		
No. (%) aged 30–40	51 (31.1)	81 (41.8)	442 (41.0)	95.06	<0.0001	84 (34.3)	110 (40.1)	587 (41.6)	96.69	<0.0001
No. (%) aged >41	81 (49.4)	59 (30.4)	190 (17.6)			111 (45.3)	83 (30.3)	263 (18.6)		
Sibling in study n (%)										
Yes	115 (70.1)	140 (72.3)	820 (76.1)	3.467	0.1767	189 (77.1)	207 (75.5)	1104 (78.2)	1.016	0.6016
No	49 (29.9)	54 (27.7)	258 (23.9)			56 (22.9)	67 (24.5)	307 (21.8)		
Comorbidity data										
No. (%) with data	161 (98.2)	180 (92.8)	1048 (97.2)			239 (97.6)	269 (98.2)	1391 (98.6)		
Other diseases n (%):				48.09 ^d	<0.0001				53.12 ^d	<0.0001
Asthma	19 (11.2)	26 (14.1)	158 (14.8)	0.3569 ^e	0.8366	55 (12.8)	64 (13.7)	363 (14.4)	1.045 ^e	0.5929
Cardiovascular disease ^f	21 (12.4)	6 (3.3)	25 (2.3)	41.25 ^e	<0.0001	43 (9.8)	25 (5.3)	73 (2.9)	20.62 ^e	<0.0001
Depression	11 (6.5)	15 (8.2)	59 (5.5)	2.626 ^e	0.2691	45 (10.4)	42 (9.0)	183 (7.3)	8.614 ^e	0.0135
Bone disease ^g	6 (3.6)	8 (4.3)	26 (2.4)	3.115 ^e	0.2106	23 (5.3)	17 (3.6)	46 (1.8)	33.35 ^e	<0.0001
No other disease	112 (66.3)	129 (70.1)	801 (74.8)			261 (60.6)	319 (68.2)	1842 (73.2)		
Social/lifestyle data										
Smoking status										
No. (%) with data	157 (96.6)	178 (91.8)	1041 (96.6)			237 (96.7)	266 (97.1)	1379 (97.7)		
Current n (%)	42 (26.7)	47 (26.4)	197 (18.9)			40 (16.9)	49 (18.4)	182 (13.2)		
Never n (%)	75 (47.8)	75 (42.1)	528 (50.7)	10.72	0.0298	122 (51.5)	142 (53.4)	691 (50.1)	11.30	0.0234
Ex n (%)	40 (25.5)	56 (31.5)	316 (30.4)			75 (31.6)	75 (28.2)	506 (36.7)		
Exposure to other peoples' smoke										
No. (%) with data	152 (92.7)	167 (86.1)	1002 (92.9)			219 (89.4)	245 (89.4)	1289 (91.4)		
Yes	92 (60.5)	78 (46.7)	495 (49.4)	7.544	0.0230	112 (51.1)	101 (41.2)	539 (41.8)	6.972	0.0306
No	60 (39.5)	89 (53.3)	507 (50.6)			107 (48.9)	144 (58.8)	750 (58.2)		
SIMD quintile at recruitment										
No. (%) with data	147 (89.6)	171 (88.1)	960 (89.1)			212 (86.5)	244 (89.1)	1264 (89.6)		
1 st (Most deprived)	26 (17.7)	28 (16.4)	71 (7.4)			37 (17.4)	32 (13.1)	113 (8.9)		
2 nd	23 (15.6)	20 (11.7)	128 (13.3)			40 (18.9)	44 (18.0)	180 (14.2)		
3 rd	18 (12.2)	34 (19.9)	165 (17.2)	30.88	0.0001	48 (22.6)	33 (13.5)	198 (15.7)	37.95	<0.0001
4 th	37 (25.2)	34 (19.9)	266 (27.7)			43 (20.3)	65 (26.6)	363 (28.7)		
5 th (Least deprived)	43 (29.3)	55 (32.1)	330 (34.4)			44 (20.8)	70 (28.7)	410 (32.4)		
Birth (SMR02) data										
Maternal height (cm)										
No. (%) with data	25 (15.2)	34 (17.5)	327 (30.3)			38 (15.9)	61 (21.6)	433 (31.6)		
Median	163.0	162.0	163.0		0.1900 ^b	160.0	160.0	163.0		<0.0001 ^b
IQR	157.5–165.0	157–166.3	158.0–166.0			155.8–163.0	156.0–165.0	159.0–166.0		
Baby SIMD quintile at birth										
No (%). with data	25 (15.2)	37 (19.1)	336 (31.2)			36 (14.7)	61 (22.3)	431 (30.5)		
1 st (Most deprived)	6 (24.0)	5 (13.5)	33 (9.8)			10 (27.8)	13 (21.3)	41 (9.5)		
2 nd	3 (12.0)	9 (24.3)	41 (12.2)			6 (16.7)	10 (16.4)	69 (16.0)		
3 rd	5 (20.0)	3 (8.1)	50 (14.9)	11.88	0.1565	5 (13.9)	6 (9.8)	82 (19.0)	12.86	0.0109
4 th	4 (16.0)	10 (27.0)	97 (28.9)			8 (22.2)	18 (29.5)	106 (24.6)		
5 th (Least deprived)	7 (28.0)	10 (27.0)	115 (34.2)			7 (19.4)	14 (23.0)	133 (30.9)		

(Continued)

Table 1. (Continued)

	Males in F ₁ -Offspring groups			X ²	P value	Females in F ₁ -Offspring groups			X ²	P value
	OMD	OFD	ONoPD			OMD	OFD	ONoPD		
Demographic data	N = 164	N = 194	N = 1078			N = 245	N = 274	N = 1411		
Parental Data										
<i>Parental Diabetes Type</i>										
Type 1	7 (4.3) ^h	3 (1.5)				12 (4.9) ^h	9 (3.3)			
Type 2	149 (90.8)	190 (97.9)	NA	10.45	0.0151	227 (92.7)	267 (96.3)	NA	5.948	0.1142
GDM	6 (3.7) ⁱ	0				4 (1.6)	0			
Unknown type	2 (1.2)	1 (0.5)				2 (0.8)	1 (0.4)			
<i>Decade of parental diabetes' diagnosis</i>										
1950–1979	2 (1.2)	1 (0.5)				6 (2.4)	2 (0.7)			
1980–1999	33 (20.1)	40 (20.6)	NA	1.383	0.7096	51 (20.8)	68 (24.8)	NA	3.732	0.2920
2000–2011	129 (78.7)	152 (78.4)				187 (76.3)	202 (73.7)			
Date unknown	0	1 (0.5)				1 (0.4)	2 (0.7)			
<i>Maternal BMI</i>										
No. (%) with data	140 (85.4)	108 (55.7)	1015 (94.2)			204 (83.2)	177 (64.6)	1318 (93.4)		
Median	30.5	27.1	25.4		<0.0001 ^b	30.5	28.0	26.0		<0.0001 ^b
IQR	26.8–35.2	23.6–31.1	23.0–29.0			26.1–35.1	24.6–32.2	23.2–29.3		
No. (%) BMI <25	21 (15.0)	38 (35.2)	453 (44.6)			42 (20.6)	52 (29.4)	543 (41.2)		
No. (%) BMI 25–29	43 (30.7)	37 (34.3)	357 (35.2)	87.24	<0.0001	50 (24.5)	60 (33.9)	496 (37.6)	114.3	<0.0001
No. (%) BMI ≥30	76 (54.3)	33 (30.5)	205 (20.2)			112 (54.9)	65 (36.7)	279 (21.2)		
<i>Paternal BMI</i>										
No. (%) with data	50 (30.5)	173 (89.2)	1033 (95.8)			78 (31.8)	247 (90.1)	1325 (93.9)		
Median	27.3	29.4	26.7		<0.0001 ^b	25.9	30.9	26.9		<0.0001 ^b
IQR	25.1–32.5	26.7–33.3	24.7–29.0			24.1–31.3	27.6–34.4	24.6–29.2		
No. (%) BMI <25	12 (24.0)	17 (9.8)	285 (27.6)			26 (33.3)	19 (7.7)	373 (28.2)		
No. (%) BMI 25–29	18 (36.0)	80 (46.2)	557 (53.9)	71.68	<0.0001	26 (33.3)	91 (36.8)	677 (51.1)	144.9	<0.0001
No. (%) BMI ≥30	20 (40.0)	76 (43.9)	191 (18.5)			26 (33.3)	137 (55.5)	275 (20.7)		

^a Chi-square and p value given from comparison with females

^b Kruskal-Wallis analysis

^c IQR denotes interquartile range

^d All 'other diseases' together

^e χ^2 and p values from each disease individually (vs. no other disease)

^f Cardiovascular disease included heart disease, hypertension and stroke

^g Bone disease included history of hip fracture, osteoarthritis and rheumatoid arthritis

^h Includes those whose mothers developed type 1 diabetes before the offspring was born (n = 8); these offspring were exposed *in utero* (EIU) to diabetes.

ⁱ Two mothers with GDM developed T2D at a later date

NA denotes not applicable

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SIMD quintile at recruitment. Material deprivation differed between groups ($P < 0.0001$ for both sexes). In males and females, higher percentages of OMD and OFD than ONoPD lived in the most deprived areas.

SMR02 (birth) data. In females, maternal height at pregnancy was lower in OMD and OFD compared with ONoPD (Kruskal-Wallis $P < 0.0001$). Higher percentages of female, but not male, OMD and OFD than ONoPD were born into the most deprived areas ($P = 0.0109$). There were no significant differences in the mother's age at pregnancy, birth-weight or season of birth between the groups.

Parental data

Parental diabetes type. The numbers of F_1 -offspring whose fathers ($n = 12$) or mothers ($n = 19$) had T1DM were too small to compare with F_1 -offspring whose fathers or mothers had T2DM (Table 1). All diabetes types were combined within the OMD and OFD groups. There was an increase in the numbers of parents diagnosed with diabetes across the decades: parents diagnosed with diabetes before 1979 all had T1DM; for parents diagnosed in 1980–1999, most had T2DM and a few had T1DM ($n = 15$), whereas the majority of the parents with diabetes (~75%) were diagnosed with T2DM after 2000.

Maternal BMI. Maternal BMI was higher in OMD than the other two groups (Kruskal-Wallis $P < 0.0001$) for both sexes. A higher proportion of OMD had mothers who were overweight (BMI of 25–29) or obese (BMI ≥ 30) than OFD and ONoPD (85% vs. 64.8% and 55.4% respectively in males; 79.4% vs. 70.6% and 58.8% respectively in females).

Paternal BMI. Paternal BMI was higher in OFD than the other two groups (Kruskal-Wallis $P < 0.0001$) for both sexes. A higher proportion of OFD had fathers who were overweight or obese than OMD and ONoPD (90.2% vs. 76.0% and 72.4% respectively in males; 92.3% vs. 66.6% and 71.8% respectively in females).

Metabolic syndrome

Higher percentages of female OMD or female OFD had MetS than female ONoPD (Table 2). In male offspring, differences did not quite reach statistical significance. Comparison of OFD with ONoPD showed higher percentages of OFD with MetS in male ($P = 0.0358$) and female ($P = 0.0285$) offspring.

We identified parameters associated with MetS in the F_1 -offspring, within each sex (Table 2). The final logistic regression model for males comprised: F_1 -offspring group, age, BMI, percent body-fat and SIMD; in females, the same parameters were used with hips, smoking status and sibling in study also included in the model. In males, predictors of MetS were: BMI (18% increased odds per kgm^{-2}) and percent body-fat (12% increased odds per percentage increase in body-fat) but not SIMD or age. In females, predictors of MetS were: OMD (78% increased odds), BMI (21% increased odds per kgm^{-2}) and age (3% increased odds per year). SIMD quintile 2 had an 89% increased odds in females but the confidence intervals were large and no other quintile had any effect.

Effects of F_0 -parental diabetes on F_1 -offspring body and biochemical measurements

MetS is a cluster of factors that increase the risk of cardiovascular disease. We concentrated on the individual criteria of MetS and the factors influencing its development in univariate analyses of body measurements, blood biochemistry and blood-pressure between the F_1 -offspring groups, for each sex (Fig 2):

Waist measurements were significantly larger in male and female OMD and OFD compared with ONoPD (Kruskal-Wallis $P < 0.0001$ for both sexes, Fig 2A).

HDL-cholesterol levels were significantly higher in female, but not male, ONoPD compared with OFD or OMD (Kruskal-Wallis $P < 0.0001$, Fig 2B).

Glucose levels were significantly higher in female, but not male, OMD compared with OFD or ONoPD (Kruskal-Wallis $P < 0.0001$, Fig 2C).

Systolic blood-pressure was significantly higher in female and male OMD compared with OFD or ONoPD (Kruskal-Wallis $P < 0.0001$ for both sexes, Fig 2D).

Table 2. Results of univariate and multivariate analysis of metabolic syndrome in the F₁-offspring groups, analysed by sex.

Univariate analysis		Males				Females				
	No. of criteria met for	Total	X ²	P value	No. of criteria met for	Total	X ²	P value		
<i>F_T</i> -Offspring group	Metabolic syndrome	(N)			Metabolic syndrome	(N)				
	0–2	≥3			0–2	≥3				
OMD n (%)	123 (88.5)	16 (11.5)	139		162 (79.4)	42 (20.6)	204			
OFD n (%)	141 (87.6)	20 (12.4)	161	5.911	0.0521	204 (88.7)	26 (11.3)	230	38.42	<0.0001
ONoPD n (%)	840 (92.5)	68 (7.5)	908	2.099 ^a	0.0358 ^a	1090 (92.9)	83 (7.1)	1173	4.798 ^a	0.0285 ^a
Total N (%)	1104 (91.4)	104 (8.6)	1208			1456 (90.6)	151 (9.4)	1607		
Logistic Regression	Response: Presence of Metabolic syndrome				Response: Presence of Metabolic syndrome					
Predictor	OR ^b	95% CI		P value	OR ^b	95% CI		P value		
<i>F_T</i> -offspring group										
OMD	0.84	0.41–1.69		0.620	1.78	1.03–3.07		0.039		
OFD	1.09	0.57–2.07		0.792	0.85	0.46–1.58		0.604		
ONoPD		Reference				Reference				
Age ^c (per year increase)	1.00	0.98–1.03		0.828	1.03	1.01–1.06		0.006		
BMI (per kgm ⁻² increase)	1.18	1.09–1.29		<0.0001	1.21	1.13–1.30		<0.0001		
Body-fat (per % increase)	1.12	1.05–1.19		0.001	1.03	1.00–1.06		0.063		
<i>SIMD</i> quintile										
1 (Most deprived)	1.84	0.79–4.25		0.155	1.66	0.82–3.36		0.155		
2	1.43	0.67–3.06		0.356	1.89	1.00–3.56		0.048		
3	1.35	0.65–2.80		0.420	1.38	0.70–2.74		0.353		
4	1.57	0.85–2.92		0.152	1.02	0.54–1.93		0.958		
5 (Least deprived)		Reference								
Hips (per cm increase)		Not included in model			1.01	0.98–1.05		0.467		
Smoking status		Not included in model			0.81	0.60–1.09		0.166		
Sibling in study		Not included in model			1.55	0.88–2.75		0.131		

Univariate and logistic regression analysis of subjects in the F₁-offspring group with metabolic syndrome (defined as 3 or more of the International Diabetes Federation criteria [18]).

Predictors with P values of <0.05 are highlighted in bold. All parameters included in the models are shown.

^a χ^2 and P values from Chi-square analysis of OFD vs. ONoPD only.

^b OR are given as per unit change in the predictor

^c Age was used as a continuous variant in the model

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Diastolic blood-pressure was significantly higher in female and male OMD compared with OFD or ONoPD; OFD had higher levels than ONoPD (Kruskal-Wallis $P < 0.0001$ for both sexes, Fig 2E).

BMI was significantly lower in male and female ONoPD compared with OMD or OFD (Kruskal-Wallis $P < 0.0001$ for both sexes, Fig 2F).

Percent body-fat was significantly higher in male and female OMD or OFD compared with ONoPD (Kruskal-Wallis $P < 0.0001$ for both sexes); in females OMD also had higher levels than OFD (Fig 2G).

There were differences between F₁-offspring groups for height, weight, hips, WHR, total cholesterol and THCR (data not shown). There were no significant differences between F₁-offspring groups for sodium, potassium, urea or creatinine.

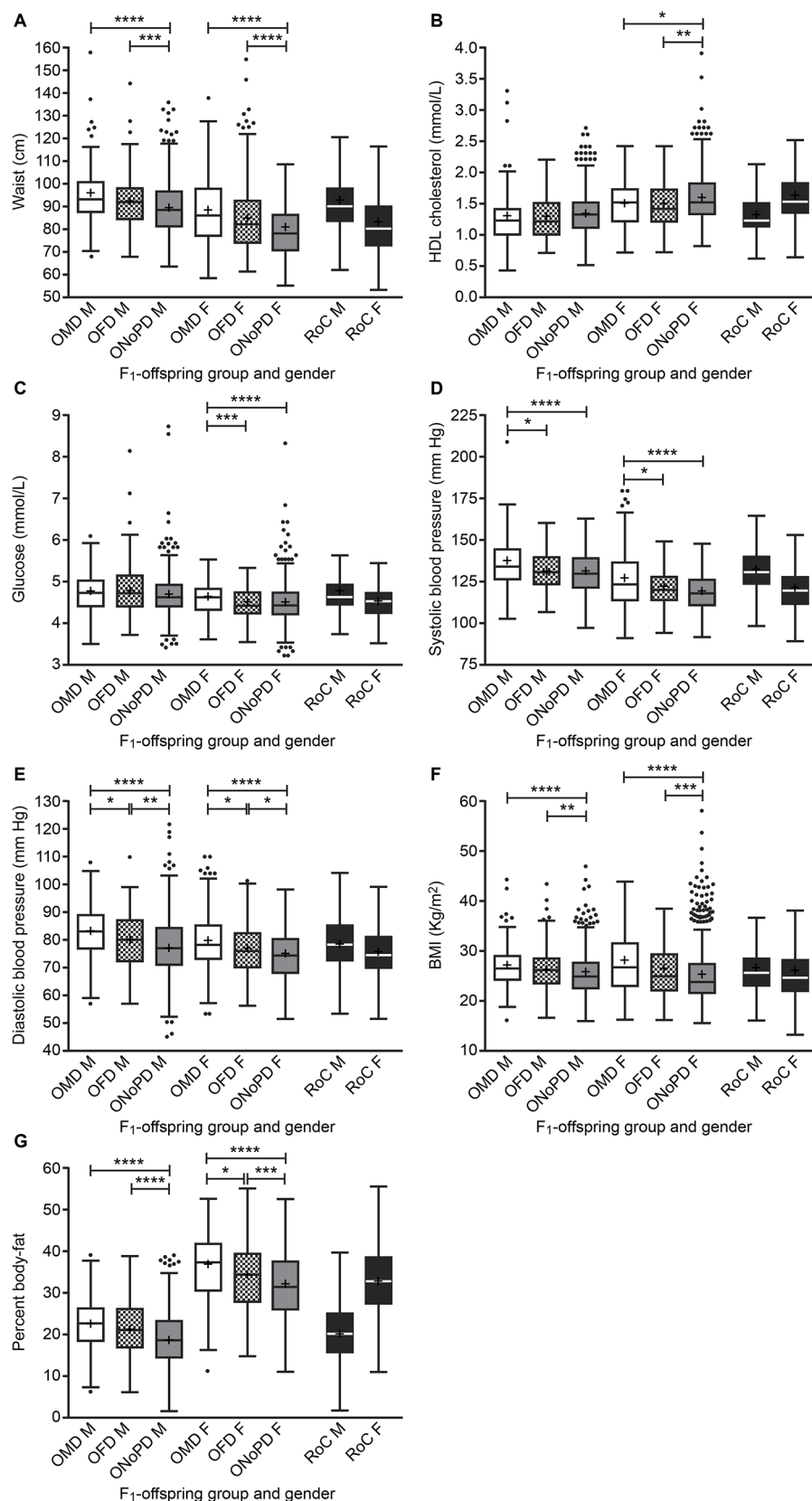


Fig 2. Body measurements, blood biochemistry and blood pressure measurements in offspring by parental group. Box-and-whiskers plots show median and IQR ('+' within the box denotes mean value) for the OMD (white boxes), OFD (hatched boxes) and ONoPD (grey boxes) in males (left) and females (right); box-and-whiskers for rest of cohort (RoC, i.e. all those without diabetes excluded from the F₁-offspring groups, [black boxes] for males and females) are also shown for comparison. Graphs are shown for Waist (A), HDL-cholesterol (B), Glucose (C), Systolic-blood pressure (D), Diastolic-blood pressure (E), BMI (F) and Percent body-fat (G). Groups were compared by Kruskal-Wallis, with level of significance between the groups indicated (* P<0.05, **P<0.01, *** P<0.001, **** P<0.0001).

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Correlation between BMI of F₁-offspring and F₀-parental BMIs

We investigated whether there were any correlations between the offspring BMIs and maternal and paternal BMIs for each of the F₁-offspring groups. BMIs of OMD significantly correlated with maternal BMIs in males ($r = 0.2264$, $P = 0.0105$) and females ($r = 0.2202$, $P = 0.0023$). However there was no correlation between BMIs of OMD and paternal BMIs in either males or females. BMIs of OFD significantly correlated with paternal BMI in males ($r = 0.2356$, $P = 0.0032$) and females ($r = 0.3838$, $P < 0.0001$). However, a significant correlation between BMIs of OFD and maternal BMIs was only seen in females ($r = 0.4167$, $P < 0.0001$) and not males. BMIs of ONoPD significantly correlated with maternal BMIs in both males ($r = 0.2271$, $P < 0.0001$) and females ($r = 0.3268$, $P < 0.0001$) as well as with paternal BMIs in both males ($r = 0.2306$, $P < 0.0001$) and females ($r = 0.2465$, $P < 0.0001$).

Intrauterine exposure to maternal diabetes

F₁-offspring exposed *in utero* (EIU) to maternal diabetes ($N = 18$) were those whose mothers developed GDM ($n = 10$) or whose mothers had pre-existing T1DM ($n = 8$) during the index pregnancy. We compared the body and biochemical measurements between EIU and other OMD: the only difference seen between EIU and the other OMD was lower diastolic blood-pressure in male EIU (Kruskal-Wallis $p = 0.0289$, data not shown).

Effect of having a grandparent with diabetes

We identified 127 F₂-grandchildren of F₀-grandparents with diabetes; all the F₀-grandparents had T2DM. The median age for all the F₂-grandchildren was 23 years (IQR 20–27). There was no difference in age for male F₂-grandchildren, but in females GMGMD and GNoGPD were significantly older than GMGFD (Kruskal-Wallis, $P = 0.0068$). The demographic and social data showed no differences when compared between the F₂-grandchildren groups by sex, apart from smoking habit, where a higher percentage of GNoGPD had never smoked and a lower percentage of GNoGPD were ex-smokers (Kruskal-Wallis $P = 0.0001$ for both sexes).

No differences in biochemical, body measurements or blood-pressure were seen when all those with a grandparent with diabetes were combined and compared with the GNoGPD group by sex, nor when grandchildren with maternal or paternal grandparents with diabetes were compared (data not shown). Differences were seen in male, but not female, grandchildren when compared by the defined grandparent groups:

Percent body-fat was significantly higher in male GPGFD ($n = 5$) than GPGMD ($n = 19$) and GNoGPD ($n = 109$, Kruskal-Wallis $P = 0.0158$);

Diastolic blood-pressure was significantly higher in male GPGMD than GMGFD ($n = 22$, Kruskal-Wallis $P = 0.0318$);

Total cholesterol levels were significantly higher in male GPGFD and GMGMD ($n = 18$) than in male GMGFD (Kruskal-Wallis $P = 0.0005$);

THCR were significantly higher in male GMGMD than GMGFD (Kruskal-Wallis $P = 0.0033$).

There were no differences in height, weight, WHR, HDL-cholesterol or systolic blood-pressure; differences in BMI, waist and hip measurements did not quite reach significance (Kruskal-Wallis, $p = 0.0790$, $p = 0.0694$ and $p = 0.0530$, respectively).

Nine grandchildren had MetS (5M, 4F) from GMGFD ($n = 2$, 5.4%), GMGMD ($n = 2$, 6.7%) and GNoGPD ($n = 5$, 2.4%) but differences were not significant. We were unable to do any further analysis of F_2 -grandchildren data due to the small numbers in each group.

Discussion

The primary aim of this study was to investigate the long-term metabolic health effects of parental diabetes on adult offspring. In females, having a mother with diabetes increased the odds of MetS. Female OMD also had lower HDL-cholesterol and higher glucose levels than the other groups. In males, the odds of MetS were not raised by maternal diabetes. Having a father with diabetes did not increase the odds of MetS in either male or female offspring. However, both male and female offspring of either parent with diabetes had raised blood-pressure, larger waists, higher BMI and increased percent body-fat than those without a parent with diabetes.

This was a cross-sectional study of a Scottish family-cohort [15,16] across two generations, rather than a birth-cohort. The data-linkage of GS:SFHS subjects with their own medical records of diabetes ensured correct classification of the F_0 -generation diabetes-status: i.e. which parent/grandparent had diabetes and date of diagnosis. We used adult offspring and grandchildren who did not have diabetes themselves to reduce any potential confounding by diabetes disease-processes on metabolic health.

The F_1 -offspring groups were not well-matched in terms of age, as OMD and OFD were significantly older than ONoPD. This is likely to be due to the diagnosis of T2DM in older parents with higher BMIs and who would, therefore, also have older offspring. It is possible, and even quite likely, that some of the parents of ONoPD will be diagnosed with diabetes in the future. We had hoped to be able to compare any effects on the offspring of the different diabetes types, but the numbers of parents with T1DM were too small. We did see a temporal effect and the increase in T2DM diagnoses in Scotland over recent years [12] was very apparent in this study.

MetS was used to indicate the severity of the parental effect and likelihood of future cardiovascular events. Only 9% of all F_1 -offspring had MetS, a level similar to the 1958 Birth Cohort [19] where prevalence was 8–9% in subjects aged 45 years, 10 years older than the median age of the F_1 -offspring in this study. Due to the lack of triglyceride measurements this level of MetS is probably under-reported, as ~30% of OMD and OFD and ~20% of ONoPD met two (of four) MetS criteria: had triglyceride data been available, the occurrence of MetS would have been higher, highlighting the increased levels of MetS in this population.

Higher percentages of both male and female OMD and OFD had MetS than ONoPD, although after adjustment for confounders, the effects of paternal diabetes on all offspring and maternal diabetes on male offspring disappeared. These data suggest that maternal diabetes independently affects the odds of MetS, equivalent to that of an increase in BMI of ~3–4 kgm^{-2} in females, and that the sex of the offspring is important. MetS was also associated with the offspring's own body measurements as BMI was a co-predictor in both sexes, while percent body-fat in males and age in females were additional predictors. The univariate analyses of the individual factors also showed differences between the OMD and other groups in females, especially for HDL-cholesterol and glucose, both criteria for MetS. Thus the sex dichotomy of MetS was borne out in its individual parameters. In males, there were fewer predictors for MetS and fewer differences in the individual parameters between groups. The particular combination of factors defining MetS may be more important than any one specific factor, in either sex. Others have also found sex-differences in the prevalence of MetS and its components in Caucasians

[20], which may also reflect sex differences in developmental programming described in animal models and human epidemiological studies [21].

Maternal and paternal diabetes showed different cardiovascular effects in F₁-offspring as, compared with OFD, OMD had higher systolic and diastolic blood-pressures in both sexes. This was also apparent in (and possibly explains) the comorbidity data at recruitment into GS: SFHS, where a significantly higher proportion of OMD had already been diagnosed with heart disease, high blood pressure or stroke, and was seen in both sexes. Longer-term studies comparing children of mothers or fathers with diabetes showed that maternal effects were stronger [2], but that offspring of fathers with diabetes had higher BMI than offspring of healthy parents [3], in accordance with our results. Similarly, circulatory diseases have been found to be more prevalent in adult offspring of mothers with any diabetes, but also present in offspring of fathers with T2DM [4]. In a mouse-model of the effects of parental diabetes on pups without diabetes, metabolic parameters were affected by maternal diabetes and worsened with age, whereas skeletal development was affected by paternal diabetes and improved with age [22]. A study of fetal malformations in diabetic-rat pregnancy suggested that the maternal environment was not solely responsible for the effects of diabetes on offspring but that paternal genetics also contributed [23]. Thus our data and these studies suggest that both maternal and paternal diabetes affect adult offspring, but that maternal diabetes has stronger effects, although mechanisms are unclear.

While maternal diabetes during pregnancy leads to higher offspring birth-weight [5,7], offspring of fathers with diabetes have lower birth-weights [10,11], as do offspring of mothers who developed diabetes >10 years after childbirth, supporting the hypothesis that genetic factors contribute to the risk of decreased prenatal growth [11]. Our birth-weight data (for offspring born 1980–1992) showed no significant differences between offspring groups, but were not corrected for gestational age. Differences may also have been masked by the average birth-weight of babies in Scotland increasing over the same time-period and the fact that mothers with diabetes also had the shortest height and highest deprivation levels, both of which reduce offspring birth-weight [24].

The long-term health effects of parental diabetes on their offspring will be affected by shared lifestyle habits, diet, physical activity and stress levels. These data were not available but we would not expect to see specific lifestyle differences between OMD and OFD. The increase in parental T2DM diagnoses between 2000 and 2011 suggest that the pre-diagnosis dietary and exercise habits of these parents may have been well-established during the childhood and adult years of the offspring. The higher material deprivation of the OMD group might also contribute to differences in diet, levels of exercise and smoking [25]. We have no information on whether either parent remained with their offspring as they were growing up. It is possible that offspring of families where the mother had diabetes may have been more influenced by the mother's diet-choices, especially if she prepared most of the family meals, than those where the father had diabetes. However, for offspring from areas of similar deprivation, we have assumed that contributions of shared lifestyle-factors would be similar in families with a mother with diabetes compared with families where the father had diabetes. The sex dichotomy within OMD is important and suggests that our results cannot be purely attributed to lifestyle similarities between parents and offspring.

We looked at parental BMI to see whether there was a relationship to that of their offspring. It was no surprise to find that maternal BMIs of OMD and paternal BMIs of OFD were higher than that of the other groups, as obesity is a key risk factor for diabetes. We did find that for the ONoPD, less than 30% of the parents had a normal BMI (i.e. of <25.0), which would suggest that a number of these parents are likely to be diagnosed with diabetes in future years. This was also true for the parent without diabetes in the OMD and OFD groups. Others have

suggested that the BMI of both parents may influence the BMI of their offspring at different ages [26,27] and also the risk of later cardiovascular disease [28]. The BMIs of both parents correlated with the BMIs of the ONoPD group but the OMD BMIs only correlated with their maternal BMIs and not the paternal BMIs. Similarly the OFD BMIs correlated with their paternal BMIs but only their maternal BMIs in females and not males. These results suggest that genetic factors from the diabetes-affected parent, may have more of an influence on the offspring than that of the other parent. A recent study of BMI has shown a parent-of-origin-effect of SNPs in specific genes on the offspring, as the effects of these SNPs within maternal and paternal alleles were in opposite directions from each other [29]. Another potential mechanism is via imprinted genes, which are those which are expressed only from either a maternally- or paternally-transmitted copy, depending on the gene in question, with the inactive allele silenced by DNA methylation [30]. A recent study has shown that offspring of obese mothers and fathers have different methylation patterns on imprinted genes compared with offspring of lean parents [31]. Such mechanisms might affect long-term body composition and may also explain some of the sex-dichotomy seen in our results. Many imprinted genes involved in fetal growth are expressed in the placenta: paternally-derived imprinted genes promote fetal growth, whereas maternally-derived genes limit fetal growth to protect maternal resources [32]. Nutrition may affect imprinted genes: female offspring of male rats fed a high-fat diet had impaired glucose tolerance and higher insulin resistance [33], possibly through epigenetic changes in sperm at conception [34]. Offspring of rats fed a high-fat diet during pregnancy had an increased risk of obesity or metabolic syndrome, a trait which was transferred to two subsequent generations through the paternal lineage [35].

The number of EIU ($n = 18$) was smaller than expected: only 0.6% of those born 1980–1992. The prevalence of diabetes in pregnancy (both GDM and pre-existing diabetes) during the same time-period was 1% in North Dakota, USA [36]. Using this rate for the SMR02-linked data gives an expected number of EIU as 27. At the current prevalence of diabetes in women of reproductive age (5% [12]), the expected number of EIU in the SMR02-linked data would be ~135. Although diabetes-related pregnancy problems were recognized in the 1960s, routine glucose-tolerance testing in pregnancy is relatively recent. Since 2010, lower glucose-thresholds for GDM diagnosis have been adopted in Scotland [37]; thus GDM that would be identified under current criteria may have remained undiagnosed, explaining our lower rate of intrauterine exposure. Despite the smaller-than-expected numbers we did not find any overall increased effect of intrauterine diabetes exposure on the offspring.

We did find some evidence that grandparental diabetes may have an effect on their grandsons' percent body-fat, total cholesterol and diastolic blood-pressure, but the numbers were too small to draw any robust conclusions. Others have shown a grandparental effect on metabolism: food-abundance in the pre-pubertal period in childhood of paternal grandfathers affected the risk of diabetes in their male grandchildren [38], while paternal grandmothers' food-abundance affected their granddaughters, but not maternal grandparents [39,40]. Potential grandparental effects need to be investigated in much larger cohorts.

In conclusion, our study suggests that maternal diabetes increases the odds of occurrence of MetS in female offspring but has less effect in male offspring. However, having a father or mother with diabetes affects body and biochemical measures and blood-pressure in adult offspring of both sexes. These results have implications for offspring of parents with diabetes, who may need to take extra care with their diet and levels of exercise to combat a predisposition for higher BMI and body-fat. This may also be particularly important for daughters of mothers with diabetes as they grow older to prevent development of metabolic syndrome.

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Author Contributions

Conceived and designed the experiments: JEN RMR RSL BHS DJP JRS. Performed the experiments: MCA AC. Analyzed the data: MCA. Contributed reagents/materials/analysis tools: AC PL. Wrote the paper: MCA JEN RMR RSL BHS DJP JRS. Obtained permissions on behalf of Generation Scotland: PL. Obtained permissions for the research: MCA.

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